A CASE OF INTESTINAL AND HEPATIC ACTINOMYCOSIS IN MAN, ASSOCIATED WITH LEUKÆMIA.

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With Pathological Report.

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Wm. H. Thomas, colored, male, was admitted to the City Hospital on November 17, 1895. He was twenty-one years old, single, and did day labor. His family history was good so far as could be learned, except that one brother was said to have died of pulmonary tuberculosis. He had been in excellent health, except for the usual ailments of childhood, up to April of 1894, when he is said to have had appendicitis, which recurred in July and again in October of the same year. Why he was not operated on for the relief of the appendicitis I do not know, nor have I any knowledge of the particulars of these attacks.

The patient first came under my observation about November 18 or 19, 1895. He was at that time slightly anæmic, complained of headache, loss of appetite, and obstinate constipation, but was not so ailing as to care to keep his bed. On November 17th, the day he entered the hospital, the evening temperature was 101°, on the following morning 100°, while on the evening of the latter day it rose to 104°, falling next morning to 98°, and again in the evening rising to 104°, with another morning fall to 98° on the 20th, but rose the same evening to 100.2°, remained at that within a fraction of a degree throughout the 21st, and on the 22d went as low as 97.6°, rising only to 98° in the evening without further decline next morning. It continued variable throughout the rest of his life, but never again rose above 103.2° or fell below 98°. Slight chills and sweats were associated with these variations in temperature. His blood was several times examined for the malarial organism, with negative results. An examination of his chest discovered nothing wrong except a feeble heart-beat. His liver, however, was found greatly enlarged, extending well below the margin of the ribs, smooth, firm, and somewhat tender. No fluctuation could be found, but a tentative diagnosis of deep-seated hepatic abscess was made. Nothing further was discovered on extending the examination to the other abdominal organs.

On November 22d he was referred to the attending surgeon, who on the 23d aspirated the liver in several places without result; whereupon I resumed charge of the case. As I still entertained the opinion that an abscess was forming, yet not sufficiently advanced to yield pus on aspiration, he was put to bed, and saline cathartics were administered to relieve constipation. No particular suffering was for some time experienced except on lying on the right side or on manipulation of the liver. This organ continued steadily to increase in size, without presenting any circumscribed area of enlargement, tenderness, or fluctuation. The diagnosis of hepatic abscess was therefore soon abandoned.

The hospital case-book records on December 14th that "the patient is unable to lie on the right side without suffering, his mucous membranes are pale, appetite poor, he is uncomfortable after eating, and bowels continue costive. Slight general anasarca present. Heart-sounds feeble, pulse weak, soft and compressible, 120 per minute." The anasarca rapidly increased, together with fluid accumulation in the peritoneal cavity. Respiration now became considerably embarrassed, without indications of direct pulmonary involvement. This dyspnœa was of greater degree than was fairly to be accounted for by interference with the movements of the diaphragm or any recognized pulmonary lesion. The respiratory difficulty, feeble heart and pulse and pale mucous membranes, with frequent nose-bleeding, suggested an examination of the blood, which was accordingly made with the following result:

Red corpuscles	3,200,000
White corpuscles	246,000
Small mononuclear leucocytes	3 per cent.
Large mononuclear and transitional leucocytes	4 " "
Polynuclear-neutrophiles	58 " "
Eosinophiles	5 " "
Myelocytes	30 " "

Proportion of white to red corpuscles 1 to 13. Hæmoglobin 25 per cent. Slight enlargement of the axillary and post-cervical lymphatic glands was now observed, but beyond this no lymphatic involvement was detected throughout the disease. Repeated examinations of the region of the spleen were made without the discovery of appreciable enlargement. The ascites was several times relieved by tapping, which added much to the comfort of the patient. Advantage was taken of the relaxed condition of the abdomen after tapping to search for the spleen, but at no time could I palpate it.

The blood examination, especially the large number of myelocytes, together with the very slight lymphatic and splenic involvement, led me to the conclusion that it was a case of almost pure myelogenous leukæmia, and that the enlarged liver was due to diffused leukæmic infiltration, as in the case described by Welch, in which the liver

attained a weight of over thirteen pounds. The patient was accordingly presented to the class, and his symptoms were considered from this point of view.

Nothing was observed in the mouth except a furred tongue at times, and extreme pallor of the mucous membrane. The teeth were white and sound, the tonsils normal, and the maxillary bones presented no surface change to attract attention, nor did the patient at any time make complaint of his mouth. No suspicion of actinomycosis was entertained, nor can I now see in reviewing the clinical history anything that could have suggested such a condition. It is possible that had an examination been made of whatever small particles were found clinging to the aspirator needle, the microscope might have cleared up the diagnosis. No such examination, however, was made.

It will be observed that at no time, while the patient was under my observation, was there anything to indicate a present appendicitis. No marked tenderness except over the liver; no lump; no intestinal disturbance except a tendency to constipation, easily relieved by cathartics without increase of pain on defecation. If any symptoms to indicate involvement of the appendix were present, they were completely masked by the condition of the liver, the ascites, and the œdema of the abdominal walls. Varying degrees and sites of pulmonary œdema were repeatedly observed during the progress of the case in the last six weeks of life, which added greatly to the respiratory labor, but which measurably diminished at times, notably after the tappings.

When the diagnosis of leukæmia was made the muriated tincture of iron, with Fowler's solution of arsenic, in twenty and five minim doses respectively, were directed. Milk punches were given three times daily, and he drank freely of milk, of which he was fond. He was not restricted to fluids, however, and at times ate the ordinary hospital fare with apparent relish, although in general his appetite was not good. As his heart was conspicuously feeble, digitalis was several times prescribed, but as this did not agree with him, strychnia sulphate, $\frac{1}{30}$ gr. three times a day, was substituted with better effect. Occasional purges were given to relieve constipation and with the hope of reducing the dropsical effusion, but with little or no effect so far as the latter was concerned, and owing to the feeble condition of the patient it was not thought expedient to persist in their use. Except the occasional administration of hypnotics and anodynes to procure sleep and relieve pain and dyspnœa, nothing further was done.

On January 15th he was tapped for the last time, with considerable relief to the dyspnœa, but for a few days only. His strength diminished steadily until February 10th, when he died, apparently from asthenia.

Autopsy about five hours after death by Prof. N. G. Keirle and Dr. John Rurah. Body of medium-sized man, development slight. General anasarca. Œdema is greater on left side of the body, face and arms especially. Skin pits on pressure everywhere. Over arms and legs fingers can be pressed in

2 cm. without difficulty. Abdomen very much distended with fluid. Thin, watery fluid running from mouth and nose. Adipose tissue scanty, and almost white in color. Blood running from veins on incision is thin and watery, and lighter in color than normal. Muscles pale and bloodless. Abdomen contains a large quantity of pale, straw-colored fluid; cavity divided into numerous spaces by adhesions, all filled with fluid. Pericardium contains about 75 c.m. of straw-colored fluid, visceral layer pale, almost white, glistening throughout. There is considerable serous effusion beneath it, giving a marked œdematous appearance. This is principally around the junction of the auricles with the ventricles. Over the left ventricle chiefly, but also over other parts of the heart surface, there are small ecchymoses about 1 mm. in diameter. Parietal layer of pericardium is white, bloodless, and glistening throughout. Heart and lungs together weigh 2190 grms. Heart weighs 340 grms. White "milk patches" on the surface of right pericardium. All cavities of heart are empty. Tricuspid orifice 33 mm. in diameter. Valve transparent, no thickening. Pulmonary artery 25 mm. in diameter. Valve transparent and perfect. Mitral orifice 31 mm. in diameter. Valve transparent throughout, with slight tendency to ground-glass appearance. Aortic orifice 23 mm. in diameter. Valve shows slight, opaque, thickened patches. Heart muscle pale and of a peculiar, translucent appearance, but no degeneration apparent to the naked eye. Coronary arteries, walls pale, otherwise normal. Thoracic aorta shows changes of slight endarteritis.

Left pleural cavity contains 500 c.c. of pale, yellowish fluid; no adhesions. On right side a few adhesions, that break up easily, between visceral and parietal layer of lower lobe. There are a few firm adhesions between lower lobe and diaphragm. Right lung pushed up to fourth rib in front, but extends in back to tenth rib. No effusions on right side. Left lung slightly pigmented, upper lobe crepitates, oozes white frothy fluid on section. Lower lobe does not crepitate in lower half, oozes a thin sanious fluid on section. Pieces sink in water. Upper lobe slightly emphysematous. Right lung also crepitates, oozes pale serum on section, upper lobe somewhat emphysematous. Middle and lower lobe solid, ooze a bloody, but pale, serum on section, not at all frothy. Pieces sink in water.

Peritoneum generally thickened, both parietal and visceral layers. Intestines bound together by peritoneal adhesions. These adhesions are divided off by numerous small spaces, all filled with fluid. Omentum very adherent and without fat; extending from right iliac fossa along right margin of the abdominal cavity to the liver, which extends some 10 c.m. below the margin of the ribs. Along the costal margin to 7 c.m. of the median line is a dense, firm mass of organized inflammatory tissue 3 c.m. in thickness. At the lower part of the same, pus escapes, on cutting out the mass, from a cavity that could not be well determined, as it was all closed in by thick walls of inflammatory tissue. Just below the liver about 25 c.c. of greenish-yellow pus escapes from an abscess at that point.

The spleen is slightly enlarged, weight 350 grms., surface bluish-gray.

Post-mortem discoloration on lower aspect; capsule slightly thickened. Spleen substance firm and the color of healthy muscle. Malpighian bodies distinct. Trabeculæ not very well marked.

Left adrenal is slightly enlarged, firm, color of healthy muscle, pigment not very dark. Right adrenal is found flattened against the liver, of brownish color, otherwise normal. Left kidney weighs 270 grms. Capsule distended with fluid, almost fell from the kidney when opened. The surface of the kidney is moderately red. Stars of Verheyen show distinctly. The cortex on section is 1 c.m. thick and irregular. Oozes a pale bloody serum. Cortical vessels indistinct. Glomeruli distinct, but pale and colorless. Irregularity in thickness of cortex apparently due to malformation. The kidney is triangular in shape, base of triangle in the pelvis. It has a swollen look, apparently cloudy swelling. Right kidney corresponds to the left, but is more regular in shape and more œdematous.

Bladder moderately distended with about 200 c.c. of urine. Its mucous membrane is very pale. Both testicles extremely pale and œdematous, with small surface cysts. Tunica albuginea remarkably white. Mesentery markedly œdematous. Sigmoid flexure and the remainder of colon to middle of transverse portion apparently normal. The entire ascending colon and the hepatic half of the transverse colon are massed in inflammatory tissue. The ascending colon, for 6 c.m. in its middle could not be removed, is black from post-mortem discoloration. The appendix is involved in a mass of inflammatory tissue just above the brim of the pelvis. Peyer's glands are distinct and present a shaven-beard appearance. Bile duct patent. Liver weighs 3260 grms. An examination of the marrow taken from the long bone of the leg shows both macroscopical and microscopical changes characteristic of leukæmia, but nothing to suggest actinomycosis.

Examination of the Liver, by Dr. W. H. Welch.

The liver was the only part submitted to me for examination. It had been incised, but was complete. It was preserved in alcohol.

Macroscopic examination. The liver presents an irregularly globular shape, measuring 22 x 18 x 12 ctm. The right lobe, which is much enlarged, is occupied throughout nearly its whole extent by a mass measuring 12 x 16 ctm. This mass extends for a short distance also into the left lobe. It extends throughout the whole thickness of the liver, from the lower to the upper surface, but it occupies a larger transverse area in the lower two-thirds than in the upper third of the organ.

The inferior surface of the right lobe, with the exception of a narrow margin of liver-substance on the right side, is entirely occupied by the new growth, which here was apparently continuous with an abscess formation extending downward along the ascending colon. This inferior surface and the posterior margin of the right lobe are connected with a dense mass of fibrous adhesions, in which are included the hepatic vessels, the right adrenal gland, and the hepatic flexure of the colon.

The diaphragm is firmly adherent to the superior surface of the right lobe of the liver, and has been removed with the liver. The mass of new growth in the liver has penetrated through the liver-substance on the upper surface, but has not penetrated through the adherent and thickened diaphragm.

Upon section it is seen that a definite fibrous capsule of dense consistence and grayish color surrounds the mass in the liver, separating it from the surrounding brownish-red parenchyma of the liver. This fibrous capsule is complete except in certain areas on the inferior surface of the liver or of the new growth, where the opaque, yellowish characteristic foci of the mass come to the surface, and were evidently in connection with the subhepatic abscess. This relation and the general topography afford presumptive evidence that the morbid process invaded the liver from below by continuity.

Upon section the mass presents in exquisite manner the characteristic honey-combed appearance of a chronic actinomycotic tumor, as is well shown in the accompanying plate. There are spaces and interlacing trabeculæ. The spaces often anastomose. They vary in shape and size on section, some being round, others oval, others more or less cylindrical. They contain a soft yellowish-white purulent material, which can be squeezed out readily, and in which can be detected abundantly the small yellowish granules of the colonies of actinomyces. The immediate margins of the spaces are of an opaque, yellowish-white, necrotic appearance. The spaces vary from 1 to 6 or 8 mm. in diameter.

The trabeculæ are in general broad and interlacing and of firm consistence and translucent gray color, like fibrous or granulation tissue.

Microscopic examination. For the study of the histological structure, staining with hæmatoxylin and eosin was used; for the details of the structure of the parasite, Gram's, Weigert's, and Mallory's stains were found most serviceable.

The microscopical sections show interlacing bands of fibrillated connective tissue, rich in long fusiform cells. Between these fibrous bands there are dense accumulations of cells. In the immediate neighborhood of the actinomyces the cells are closely packed together and there is little or no basement substance. These cells are predominantly polynuclear leucocytes; in other words, the parasitic colonies lie for the most part in purulent foci. Outside of the areas of actual pus there is granulation tissue in varying stages of formation, from a tissue composed almost exclusively of granulation cells and leucocytes to a tissue rich in basement-substance and with elongated cells. In the fibrous trabeculæ are bloodvessels with thick muscular walls, and containing an excess of leucocytes, among which are many mononuclear forms. Adjacent to the liver parenchyma the fibrous tissue is dense and contains numerous rows of compressed liver-cells, presenting the appearance of the so-called newly formed bile-ducts. Here and there are mucous glands derived from those in the walls of the bile-ducts, but now without evident connection with bile-ducts, and apparently hypertrophied

and proliferating so as to simulate adenomata. The capillaries of the liver contain an excess of leucocytes, mononuclear cells predominating.

The colonies of actinomyces are rarely single, more frequently they are conglomerated into irregular masses, which may be 1 to 2 mm. in diameter. These colonies in general present a central, looser part of tangled fine filaments and slender rods, with, at times, deeply staining coccus-like bodies, and a more densely woven ring of fine filaments nearer the periphery, from which the filamentous branching threads radiate outward. These radiating threads often extend out among the surrounding pus-cells and are often devoid of any bulbous swellings or club-like extremities.

It was not found easy to demonstrate satisfactorily the clubs which are frequently found at the extremities of the threads in cases of actinomycosis. The stain recommended by Mallory is most suitable for this demonstration. By this stain there could be demonstrated around some, although not around most, colonies a deeply stained red, almost homogeneous, peripheral zone, into which the blue threads could be traced. This red margin clearly belonged to the parasite and not to the surrounding cells, from which it was often separated by a narrow space. The outer surface of this red border was often somewhat irregular and indented, and in general the impression was gained that this outer zone, which stained by Mallory's method deeply red, consisted of the coalesced material which composes the club-like swellings at the extremities of the threads in most cases of actinomycosis. I am inclined to interpret the failure to demonstrate sharply defined clubs in this case, and the appearance of a diffuse, homogeneous, peripheral substance, with the staining reactions of the clubs, to post-mortem changes. That the clubs may become indistinct or even disappear in consequence of post-mortem changes has been demonstrated by Weigert.

But only some of the colonies showed this homogeneous marginal zone. Many were entirely devoid of such a zone or of any suggestion of clubs. It is now well known that actinomyces colonies are often devoid of the characteristic club-like swellings. In this case, as in that reported by Mallory, there were numerous bacilli belonging to the actinomyces, scattered among the cells independently of the colonies. Clumps of streptococci were also observed in small number, so that there was mixed infection with actinomyces and streptococcus.

The mass in the liver, therefore, presents macroscopically and microscopically the typical structure of an actinomycotic tumor. As has already been stated, the evidence is that the parasite gained access to the liver and generated the new growth at the inferior surface of the organ. The process gradually extended so as to invade most of the right lobe and a part of the left lobe of the liver.

Although I have not had the opportunity to examine other parts from this case, there can be little or no doubt, in the light of the clin-

ical history and the observations made at the autopsy, and in similar cases, that the portal of entry of the parasite was the intestine, and in all probability the starting point was actinomycotic appendicitis (possibly colitis), whence the morbid process extended upward in the tissues along the ascending colon to the right hypochondrium, and invaded the liver at its lower surface. (End of Dr. Welch's report.)

The coexistence of leukæmia with actinomycosis has not, I believe, been noted, and it would be of interest to determine if they may sustain any etiological relation to each other. I cannot find in any of the reports that have come to my notice any reference to examinations of the blood in actinomycosis, except for the specific organism, which has not, I believe, been found in it. Nor do I find any reference to general conditions analogous to those occurring in leukæmia that might not be accounted for as the result of the local development. It seems rational, therefore, to conclude that this complication was purely accidental. It must, however, have told very much on the progress of the case, no doubt hastening the end and adding materially to the suffering of the patient. The labored breathing, although in part accounted for by the condition of the left lung, the small pleuritic effusion, the recurring pulmonary œdema, the pressure of the liver and of the ascitic fluid, was doubtless largely due to the defective oxygen-carrying capacity of the blood. So no doubt the unusual extent of the dropsy, affecting nearly every organ and tissue of the body as it did, was rather of leukæmic than actinomycotic origin. No board-like œdematous infiltration such as has been noted with pulmonary actinomycosis was observed, but everywhere a diffuse serous infiltration of ordinary character.

To the leukæmia must also be referred in great part the marked feebleness of the patient beyond what is usually observed in actinomycosis, although this was also to some extent due to the septic condition, of which the alternating irregular fevers, chills, and sweats were indications.

The mode of entrance of the infecting organism in this case seems clearly to have been by the alimentary canal. The parasite effected a lodgement in the vicinity of the appendix, where its primary development occurred. This conclusion is warranted by the post-mortem observations as well as by the clinical history and by

previous reports of cases of actimycotic appendicitis. The patient, living alternately in the country and in the city, was no doubt while in the former in position to acquire the habit of carelessly chewing grains and other vegetable matter, and may have been in close association with infected cattle; but as no suspicion of the real nature of the trouble was entertained during his life, nothing was learned tending to show clearly the source of infection. There is strong reason for doubting whether the disease may be directly communicated from cattle to man by simple contact; indeed, inoculations of lower animals have been attended with such imperfect success as to make this source of infection unworthy of belief. No case of direct transmission, even from cow to cow, has been shown. Nor is there any evidence that the disease may be acquired by eating the flesh of infected animals, and the fact that its existence has been reported in but one of the carnivora—a dog—goes far to show that this is a most unlikely mode of propagation. The same may be said of milk as a source of infection. Bollinger had one case, primary in the brain, attributed by him to milk infection.

The disease has rarely been observed on the udder or teats of cows. Leith[1] refers to an interesting case of infection of the milk glands of the cow, which he was enabled to examine through the kindness of Prof. Mettam, in which the characteristic elements of actinomycosis were found lying among the galactophorous ducts, which, however, they did not invade. The tubes, notwithstanding, showed marked signs of disease, "their living epithelial cells being greatly swollen, staining badly, and being without nuclei. There is also in places a considerable amount of interstitial round-celled infiltration. It is thus seen that the actinomyces does not itself apparently directly invade the gland tubes in this case. It produces a considerable change in them of a hurtful character, and further, that it is difficult to believe that the parasite does not in some form or other directly invade the tubes, as the two lie so close together and are so intermingled."

Against its transmission to human beings by milk—the possibility of which must be admitted—is its extreme rarity in early childhood. Only four cases in Leith's series of 378 cases occurred prior to the fifth year, and only seven up to the tenth year.

[1] Edinburgh Hospital Reports, vol. ii. p. 179.

Plate 1 missing

Pages 337-end missing